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Palovarotene Clinical Program Update

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2016 FOP Friends, UK Conference & Family Gathering

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Palovarotene Development Program

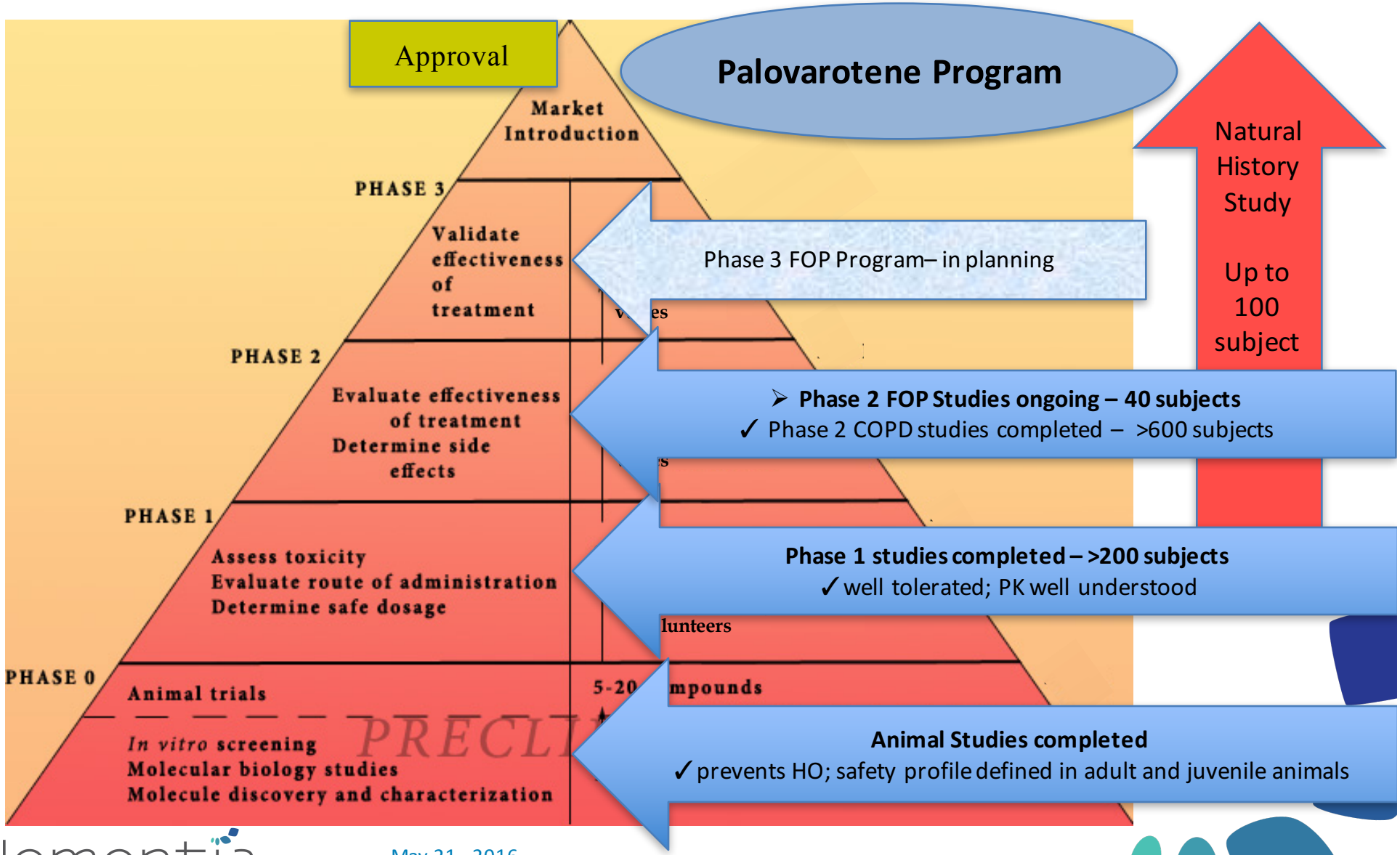
Objective: Provide sufficient data for regulatory review/approval of palovarotene for the treatment of FOP in adults and children

Key activities necessary to accomplish objective:

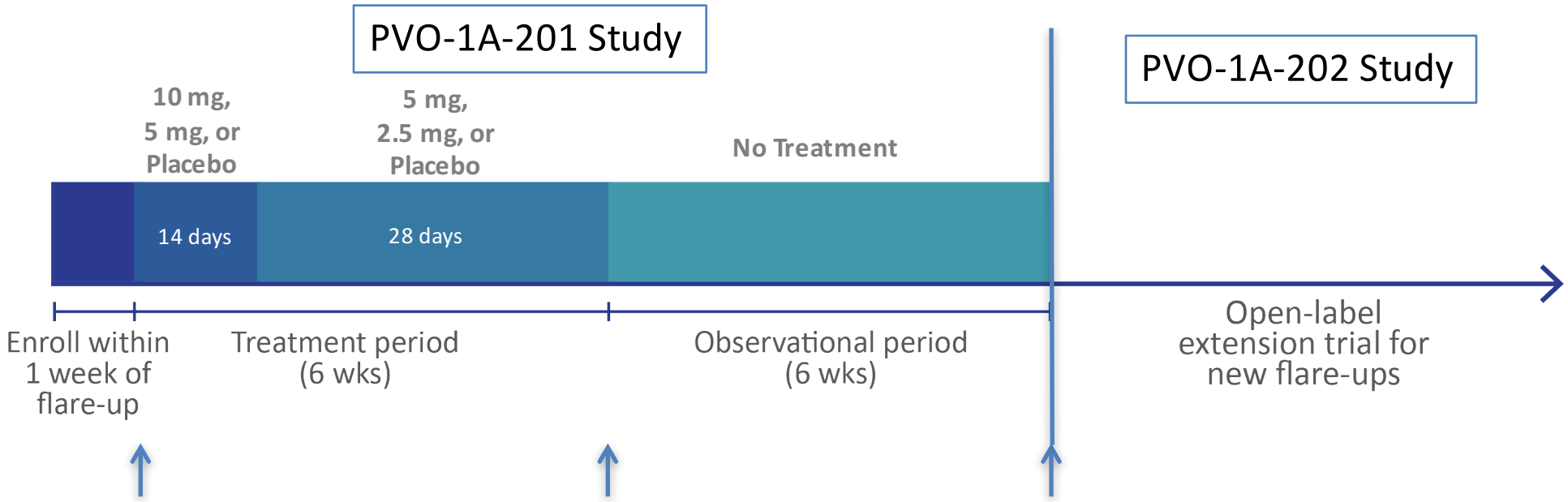
- Understand how the molecule may impact FOP
- Determine the effects in animal models of FOP
- Determine the toxicity in animals
- Understand the course of FOP and flare-ups
- Determine the pharmacokinetics and safety in healthy volunteers
- Explore ability of various doses to prevent HO
- Confirm the efficacy in preventing HO
- Evaluate safety and tolerability at the doses that are necessary to prevent HO

Drug Development Pathway

Where Are We With Palovarotene?



Phase 2 Program in FOP: An Overview



Primary endpoint:

% responders, (no or minimal new bone formation by X-ray at 6 weeks)

Imaging endpoints

- X-ray
- CT scan
- MRI or ultrasound (US)

Functional endpoints

- FOP Patient Reported Outcome (PRO)
- Range of motion
- Global Health scales

Symptom and other measures

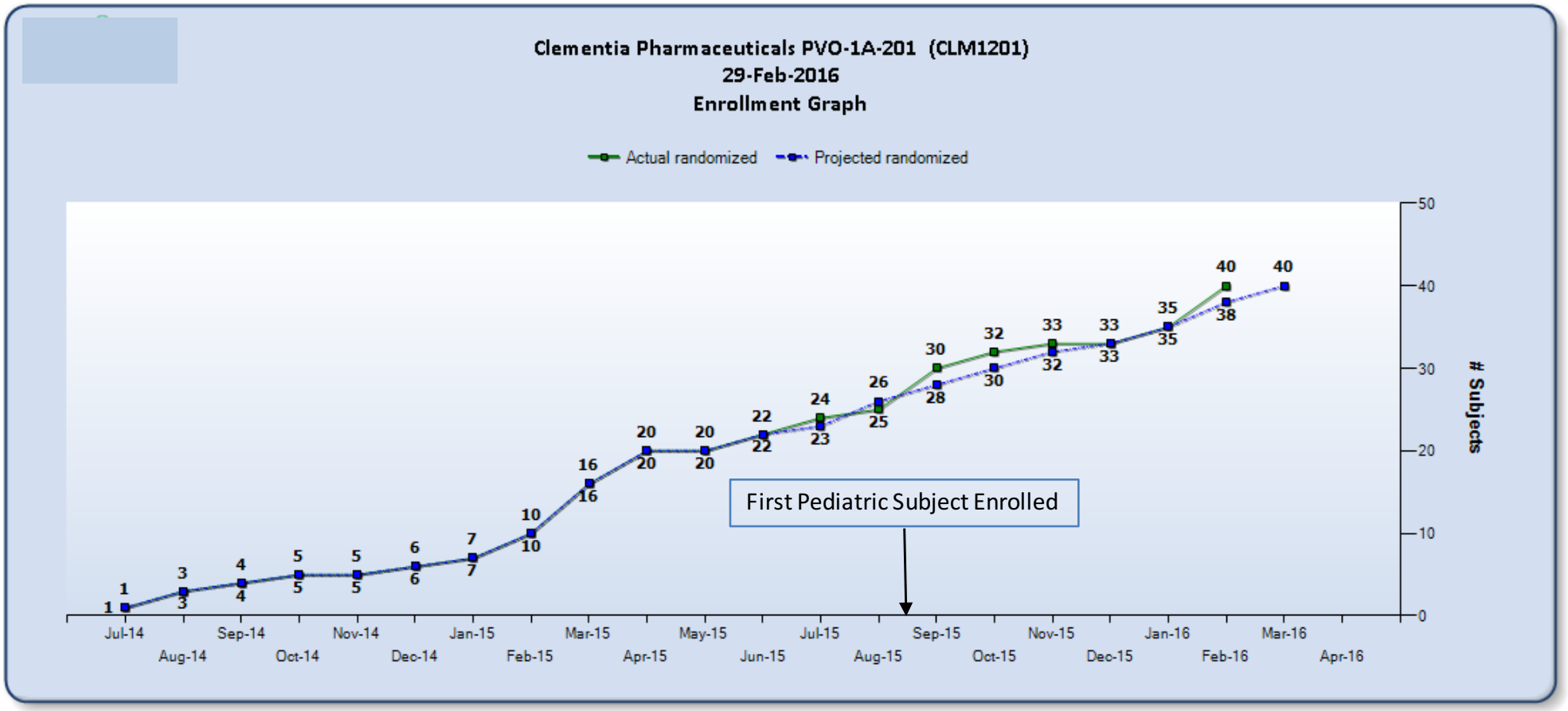
- NRS pain and swelling
- Cartilage, bone and inflammatory biomarkers
- Device questionnaire

- Randomized, double-blind, multicenter, placebo-controlled (3:1 randomization)
- Adaptive (for dose, duration and timing of assessments)
- All subjects successfully completing 12 week DB trial can participate in OLE

Phase 2 Study – PVO-1A-201

Recruitment

- Enrollment Complete- 40 subjects enrolled (28 adults; 12 children)!
- Enrollment average over entire study was 2 subjects/month



Phase 2 Study - PVO-1A-201

Baseline Characteristics/Flare-up locations

- 40 subjects enrolled
  - Average age: 22 years (range 7-53)
  - 46% male
- Flare-up Locations:
  - Shoulder – 4
  - Elbow – 4
  - Wrist – 2
  - Abdomen – 1
  - Hip/thigh - 17
  - Knee - 9
  - Ankle – 2
  - Chest – 1
- 1 subject ongoing; all subjects completing 12-week study have enrolled into open label extension

Phase 2 Interventional Trials

Lessons Learned to Date

- Well designed and executed patient assessment, travel and at-home care has allowed for timely enrollment of subjects across the globe
  - The 40 subjects have come from 12 different countries (US, Canada, Argentina, Brazil, Venezuela, France, England, Northern Ireland, Netherlands, Spain, Australia, India)
  - Travel has included car, airplane, and air ambulance
  - Accompanied by up to 2 caregivers (and occasionally siblings)
- Able to enroll subjects (except 1) within the 7 day flare-up start window
- All subjects able to undergo flare-up site specific x-ray and CT scan (except 1)
- Large proportion of subjects unable to undergo MRI imaging – added ultrasound (US) to protocol for edema assessment

Phase 2 Interventional Trials

Lessons Learned to Date

- Substantial flare-up symptoms reported by subjects across both studies
  - Most common: pain (95%), swelling (69-77%), stiffness (55-74%), decreased range of motion (41-62%), and warmth (46-51%)
  - 46-67% reported at least 4 symptoms
- Current palovarotene dosing regimens are well tolerated with no safety issues identified
  - No subject discontinued treatment or required reduction of dose
- Low dose CT scan more sensitive than x-ray in identifying new HO
- Vast majority of flare-ups that formed new HO developed it by 6 weeks

Next Steps

- Complete subject participation in Phase 2 study (-201)
- Complete collection of all the data, ensuring accuracy
- Analyze results
- Report high level results to FOP community – Fall 2016
- Once dose response established, utilize data (including NHS data) to finalize design and initiate Phase 3 program:
  - Study to confirm prevention of HO
  - Study to evaluate preservation of movement after surgical removal of HO

Sincere gratitude to the patients/families, clinicians/researchers who have given their time and effort to this quest!